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EXAMINER	
BRISTOL, LYNN ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,971	KOJIMA, TETSUO	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/17/04;9/15/05; 5/25/06; 3/29/07 .

DETAILED ACTION

1. Claims 1-18 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election without traverse of Group IV (Claims 15-17) in the reply filed on 5/31/07 is acknowledged.

3. Claims 1-14 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/31/07.

4. Claims 15-17 are all the pending claims under examination.

Information Disclosure Statement

5. The references cited in the IDS' of 5/25/06 and 3/29/07 have been considered and entered. The Examiner acknowledges Applicants explanation of the foreign language references, AD and AE, on p. 1 of the IDS of 5/25/06.

6. The information disclosure statements filed 12/17/04 and 9/15/05 fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. The IDS' of 12/17/04 and 9/15/05 recite the same references cited in the IPER for the corresponding parent PCT application, however, no copies of the cited

references are enclosed with either IDS. The references in the 1449 forms have been stricken to indicate that they have not been considered.

7. The information disclosure statements filed 12/17/04 and 9/15/05 fail to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, *or other information* submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

The 1449 forms do list the enclosed copy of the IPER as a reference, and a copy of the IPER was received with each IDS.

Specification

8. The guidelines in 37 CFR 1.77(b) illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use. A "DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)" should be inserted between the "SUMMARY OF THE INVENTION" and the "DETAILED DESCRIPTION OF THE INVENTION." In the instant case, the "Brief Description of the

Drawings" appears after the Detailed Description of the Invention" on p. 21 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: preparing and/or introducing an expression vector into the method steps. Alternatively, if Applicants intended claim scope is for introducing the first VH and VL domains and the second VH and VL domains into an expression vector, then the claims omit the step of subcloning the domains into the vector.

b) Claims 15 and 17 are indefinite for the recitation "with a long linker" because the term "long" is relative term and is not defined by the claims. The specification defines the linker on p. 12, lines 8-21, and more specifically a "long linker" at lines 11-17. The linker length is defined in the specification by preferable size ranges. It appears that a requirement for a "long linker" is that it "enables the antibody VH and VL domains

to be present as a scFv when the domains are combined with the linker are expressed in a phage library."

c) Claim 15 is indefinite for the recitation "the other ends comprise a restriction enzyme site" in element b) because it is not clear if the "other ends" refers to the unlinked ends for either one or both of the VH domain and the VL region.

d) Claim 15 recites the limitation "the fragments obtained from the above treatment" in element d). There is insufficient antecedent basis for this limitation in the claim.

e) Claim 15 recites the limitation "the heavy and light chain variable domains against the second antigen" in element d). There is insufficient antecedent basis for this limitation in the claim because element b) recites "a light chain variable *region*" directed against "a second antigen."

f) Claim 16 recites the limitation "the gene" in elements a) and c). There is insufficient antecedent basis for this limitation in the claim or in Claim 1 from which the claim depends.

g) Claims 15- 17 are indefinite for the recitation in elements a) and b) of Claim 15 and element a) in Claim 17 "constructing an antibody phage library in which a light chain variable domain and a heavy chain variable domain...restriction enzyme sites" because it is not clear how only one VL and VH can comprise an antibody library, when a plurality of VL/VH pairings would seemingly be required to comprise the library.

h) Claim 17 recites the limitation " the fragments obtained above" in element c). There is insufficient antecedent basis for this limitation in the claim.

i) Claim 17 is indefinite for the recitation "both against an antigen" because it is not clear if the VH and VL domains should bind the same or a different antigen. The embodiments disclosed are for diabodies where scFvs are cross-paired and one scFv recognizes one antigen and the other scFv recognizes a different antigen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claim 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGuinness et al. (Nat. Biotech. 14:1149-1154 (1996)) and Volkel (Protein Engineering 14(10):815-823 (2001); cited in the IDS of 5/25/06).

Claims 15 and 16 are drawn to a method for constructing an antibody phage library or expression vector, comprising constructing an antibody library with a VL and VH domain against a first antigen and connected with a long linker comprising a

restriction enzyme site, and an antibody library with a VL and VH domain against a second antigen and connected with a long linker where the other ends comprise a restriction site, treating the libraries or genes comprising the variable domains with a restriction enzyme, and performing ligation of the fragments to construct a fragment in which the VH and VL against the second antigen are inserted between the VL and VH against the first antigen, *or* treating the gene with a restriction enzyme, and treating a gene encoding two Ab variable domains where both ends comprise a restriction enzyme site with a restriction enzyme, and inserting the gene from the second digest into the gene from the first digest.

Claim 17 is drawn to a method for constructing an antibody phage library or expression vector, where the library is constructed from a VL domain and a VH domain, both against an antigen and being connected with a long linker comprising two restrictions enzyme sites, treating the library of genes comprising the variable domains with a restriction enzyme and performing self-ligation of the fragments obtained in order to shorten the linker between the variable domains.

The claims were prima facie obvious at the time of the invention in view of McGuinness and Volkel.

McGuinness discloses methods for constructing an antibody phage display library where the V regions from antibodies against the hapten phOX or Dig are constructed into two pools of scFvs repertoires having a 15-amino acid linker between each VH and VL domain, where the orientation of the domains is VH-linker-VL (p. 1150, Col. 1, ¶1). The scFv pools were recombined into a diabody format: VHA-VLB-rbs

(linker)-VHB-VLA, where the linker between each VH and VL domain was "shortened" to a zero linker (p. 1150, Col. 2, ¶1) using one of two methods: ligation mediated assembly or cassette cloning where the final diabody is inserted into an expression vector.

For ligation-mediated assembly, a two- (Fig 21, A-C) or three-step (Fig. 2iD) process is taught in the Materials and Methods on p. 1153, ¶2. In the three-step approach, an 800 bp fragment comprising Dig VH-phOxVL and phOxVH fragment are cut with a restriction enzyme and ligated, then the ligated fragment was mixed with a Dig VL fragment and digested with another restriction enzyme, and then ligated to produce the diabody insert. The two-step approach comprised taking the 800 bp fragment comprising Dig VH-phOxVL and phOxVH and a phOxVH-DigVL fragment, ligating the mixture and digesting with restriction enzymes to produced the diabody insert.

For cassette cloning, VHA-VLB and VHB-VLA fragments were generated by PCR extension from the scFv pools, and the fragments digested with different restriction enzymes (Fig. 2ii) to produce a DigVH-phOxVL fragment and a phOxVH-DigVL fragment with terminal restriction sites followed by assembly into the diabody (p. 1151, Col. 1, ¶2; and M & M, p. 1153, Col. 2, ¶2).

The 15 amino acid linker of McGuinness is considered as reading on the linker for the first and second single scFvs of Claim 1 and the HV and LV of Claim 17. The claims are not drawn to the specific order in which the VH1 and VL1 or the VH2 and VL2 should occur. In other words, McGuinness teaches a diabody format: VHA-VLB-rbs

(linker)-VHB-VLA which reads on the instant claims. The method steps of subcloning fragments and digesting the fragments with enzymes to arrive at the diabody structure is not excluded by claims 15-17, therefore, the steps of McGuinness read on the claims.

Volkel discloses constructing a diabody phage display library comprising single chain diabody CEA scFv/Gal scFv with a randomized middle linker from where the M linker is of variable length and comprises at least one restriction site (See Figure 2A and B). Volkel discloses generating a fragment comprising GalVL-M linker- GALVH where the M linker comprises a restriction site and subcloning the fragment into the linker region for the CEA scFv where the linker region comprises two restriction enzyme sites, BstE II and Sac I. Volkel discloses generating clones with variable linker and M-linker lengths and comprising different amino acid sequences (Tables III and IV) which are cloned into an expression vector.

One skilled in the art would have been motivated and been assured of reasonable success in having produced the instant method at the time of the invention based on the combined disclosures of McGuinness and Volkel because each disclose the technology for constructing single-chain diabody phage display libraries where a scFv recognizing a first antigen comprising a linker with a restriction enzyme site and a second scFv recognizing a second antigen comprising a linker are treated with a restriction enzyme in order to obtain fragments which are then ligated in order to construct a final fragment having the VH and VL domains against the second antigen inserted between the VH and VL domains against the first antigen are assembled into the diabody phage display library. Each of the references discloses techniques involving

differential restriction enzyme digestion of various fragments and the technology for selective insertion of the VH2/VL2 or VL2/VH2 pair between the VH1/VL1 or VL1/VH1 domains to generate a phage display diabody library. Each of the references teaches obtaining fragments comprising variable domains and shortening the linker between the domains in a ligation (PCR extension step). Based on the combined reference disclosures, one skilled in the art could have been assured of success in introducing linkers between VH and VL domains comprising restriction sites for subcloning into or between VH and VL domains against a different antigen because the references taught that subfragments could readily be generated and where a VH/VL pair against one antigen was inserted between the VH and VL against a different antigen. McGuinness teaches that construction and selection from such a library is possible and it avoids unfavorable combinations (p. 1153, Col. 1, ¶2), and Volkel discloses generating single-chain diabodies with optimized linker sequences and expressed by phage display where correctly folded molecules can be screened against a variety of different target cells and antigens (p. 822, Col. 2, ¶3).

For all of the foregoing reasons, the claimed method at the time of the invention was prima facie obvious to one of ordinary skill in the art over the combined reference disclosures of McGuinness and Volkel.

Conclusion

11. No claims are allowed.

12. The CA 2331641 (published 11/11/99) patent reference is cited in the IDS of 5/25/07 is considered relevant but not relied by the Examiner.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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